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The Burden of Parasitic Zoonoses in Nepal: A Systematic Review

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Abstract

Background: Parasitic zoonoses (PZs) pose a significant but often neglected threat to public health, especially in developing countries. In order to obtain a better understanding of their health impact, summary measures of population health may be calculated, such as the Disability-Adjusted Life Year (DALY). However, the data required to calculate such measures are often not readily available for these diseases, which may lead to a vicious circle of under-recognition and under-funding.

Methodology: We examined the burden of PZs in Nepal through a systematic review of online and offline data sources. PZs were classified qualitatively according to endemicity, and where possible a quantitative burden assessment was conducted in terms of the annual number of incident cases, deaths and DALYs.

Principal Findings: Between 2000 and 2012, the highest annual burden was imposed by neurocysticercosis and congenital toxoplasmosis (14,268 DALYs [95% Credibility Interval (CrI): 5450–27,694] and 9255 DALYs [95% CrI: 6135–13,292], respectively), followed by cystic echinococcosis (251 DALYs [95% CrI: 105–458]). Nepal is probably endemic for trichinellosis, toxocarosis, diphyllorhynchosis, foodborne trematodosis, taeniosis, and zoonotic intestinal helminthic and protozoal infections, but insufficient data were available to quantify their health impact. Sporadic cases of alveolar echinococcosis, angiostrongylosis, capillariosis, dirofilariosis, gnathostomosis, sparganosis and cutaneous leishmaniasis may occur.

Conclusions/Significance: In settings with limited surveillance capacity, it is possible to quantify the health impact of PZs and other neglected diseases, thereby interrupting the vicious circle of neglect. In Nepal, we found that several PZs are endemic and are imposing a significant burden to public health, higher than that of malaria, and comparable to that of HIV/AIDS. However, several critical data gaps remain. Enhanced surveillance for the endemic PZs identified in this study would enable additional burden estimates, and a more complete picture of the impact of these diseases.

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Introduction

Various parasites infecting humans depend on vertebrate animals to complete their life cycle. Humans most commonly become infected with these zoonotic parasites through consumption of infected hosts or through fecal-oral contamination. The results of these infections may vary from asymptomatic carriage to long-term morbidity and even death. Although data are still scarce, it is clear that these parasitic zoonoses (PZs) present a significant burden for public health, particularly in poor and marginalized communities [1,2]. Moreover, PZs can lead to

significant economic losses, both directly, through their adverse effects on human and animal health, and indirectly, through control measures required in the food production chain [3,4].

Estimates of the impact of diseases on public health, generally referred to as burden of disease, may be valuable inputs for decision makers when setting policy priorities and monitoring intervention programs. In Nepal, it is now recognized that health sector needs should be prioritized, and that disease burden should be considered as one of the bases for this prioritization [5]. However, disease burden estimates are not readily available. While the World Health Organization and the Global Burden of Disease

Author Summary

Various parasites that infect humans require animals in some stage of their life cycle. Infection with these so-called zoonotic parasites may vary from asymptomatic carriership to long-term morbidity and even death. Although data are still scarce, it is clear that parasitic zoonoses (PZs) present a significant burden for public health, particularly in poor and marginalized communities. So far, however, there has been relatively little attention to this group of diseases, causing various PZs to be labeled neglected tropical diseases. In this study, the authors reviewed a large variety of data sources to study the relevance and importance of PZs in Nepal. It was found that a large number of PZs are present in Nepal and are imposing an impact higher than that of malaria and comparable to that of HIV/AIDS. These results therefore suggest that PZs deserve greater attention and more intensive surveillance. Furthermore, this study has shown that even in settings with limited surveillance capacity, it is possible to quantify the impact of neglected diseases and, consequently, to break the vicious circle of neglect.

(GBD) initiative have generated such estimates for Nepal, these were largely based on regional extrapolations, and, more importantly, included only a limited number of PZs [6,7]. If disease burden estimates are to be used for priority setting, an incomplete assessment of the burden of PZs may lead to a vicious circle of under-recognition, a wrong ranking of priorities and under-funding for research, prevention and control programs [8].

To address this issue, a disease burden assessment of PZs was conducted in Nepal. Ideally, the primary data sources for such studies would be official surveillance data and death registers. In Nepal, however, these data sources have limited value in terms of PZs. The official passive surveillance system of the Government of Nepal, the *Health Management Information System* (HMIS), has been reported to suffer from inconsistencies, incomplete reporting, and under-reporting from mainly central-level and private hospitals [9,10]. Active surveillance systems are in place, but only target certain vaccine-preventable diseases, and not PZs. Death registration is reported to have a completeness rate of 32% [11]. We therefore opted for a more comprehensive approach, based on a systematic review of all possible secondary data sources related to PZs in Nepal from 1990 to 2012. This comprehensive review allowed us to identify endemic and possibly endemic PZs, and, subsequently, to quantify the disease burden of those PZs for which sufficient quantitative data were available.

Materials and Methods

The main objective of this study was to provide a comprehensive overview of the public health impact of PZs in Nepal. To this end, a step-wise approach was taken:

- (1) Systematic review of national and international peer-reviewed and grey literature;
- (2) Qualitative assessment: classification of considered PZs according to (presumed) endemicity status and data availability; and
- (3) Quantitative assessment: quantification of health impact of endemic PZs in terms of the annual number of cases, deaths and Disability-Adjusted Life Years (DALYs), for the year 2006.

Considered PZs

The twenty PZs considered in this study are listed in Table 1. This selection is based on a recent review of the world-wide socioeconomic burden of PZs [1] and a review of emerging food-borne parasites [12], as many PZs may be classified as being food-borne. Seven of the considered PZs also belong to the group of neglected tropical diseases, i.e., leishmaniasis, cystic and alveolar echinococcosis, cysticercosis, food-borne trematodosis, schistosomiasis and soil-transmitted helminthosis [13,14].

Systematic review

Direct and indirect evidence on the occurrence of the considered PZs was located through a systematic search of national and international peer-reviewed and grey literature. Direct evidence was defined as any data on prevalence, incidence or mortality of the PZ in humans. Indirect evidence was defined as occurrence of the concerned parasite in animal hosts or in the environment (e.g., water, soil). If no direct or indirect evidence could be identified from Nepal (further referred to as “local” evidence), recent case reports were sought from (North) India, Nepal’s largest neighbor with whom it shares an open border in the west, south and east, and from the Tibet Autonomous Region, which borders Nepal in the north (Figure 1).

For each PZ, we constructed a search phrase consisting of the key word “Nepal” and any element of a list containing the name of the PZ, possible synonyms, and the name(s) of the causative parasite(s) (Table S1-1 in Supporting Information S1). Manuscript titles were retrieved through searching PubMed, Web of Science, WHO Global Health Library, Asia Journals OnLine (AsiaJOL) and MedInd. If available, the major Nepalese journals were additionally searched through their websites (Table S1-2 in Supporting Information S1). In addition, the thesis libraries of Tribhuvan University (Kathmandu, Nepal) and the Institute of Animal Agriculture Sciences (Rampur, Chitwan district) were manually explored to find relevant manuscripts. Dissertations were also collected from the website of the Veterinary Public Health master course jointly organized by Chiang Mai University (Thailand) and Freie Universität Berlin (Germany), as this program has a regular intake of Nepalese students. No dissertations were sought from countries neighboring Nepal, as we did not have prior knowledge of masters courses organized in these countries with a regular intake of Nepalese students.

In a second step, the retrieved titles were screened for eligibility by applying a set of predefined criteria to the titles and, if possible, to the abstracts and full texts. Only papers published in 1990 or later were considered eligible, and no restrictions were placed on the language of publication. For the qualitative assessment, documents were only excluded if they did not relate to the PZ in question, or if they did not pertain to Nepal or Nepalese patients. For the quantitative assessment, additional restrictions were put on the year of publication (between 2000 and 2012), the study setting and population (Nepalese patients infected in Nepal), and the type of information (quantitative, thus excluding case reports and case series). Finally, additional titles were sought for using forward and backward reference searches (so-called “snowballing”). In the forward reference search, the titles eligible for the qualitative assessment were entered in Google Scholar (<http://scholar.google.com/>) to obtain a list of articles citing the former. The latter were then screened using the same criteria as used in the initial searches. In the backward reference search, the reference lists of the initially retrieved eligible documents were hand-searched and the same criteria were applied. The forward and backward searches were repeated until no more new

Table 1. Parasitic zoonoses considered in the Nepalese burden of disease study (in alphabetical order).

Parasitic zoonosis	Involved species	Transmission route(s)*
Alveolar echinococcosis	<i>Echinococcus multilocularis</i>	Fecal-oral
Angiostrongylosis	<i>Angiostrongylus cantonensis</i>	Snail-borne (meat-borne, fecal-oral)
Anisakidae infections	<i>Anisakis</i> spp., <i>Pseudoterranova</i> spp.	Fish-borne
Capillariosis	<i>Capillaria philippinensis</i>	Fish-borne
	<i>Capillaria hepatica</i>	Meat-borne
	<i>Capillaria aerophila</i>	Fecal-oral (earthworm-borne)
Cystic echinococcosis	<i>Echinococcus granulosus</i>	Fecal-oral
Cysticercosis	<i>Taenia solium</i>	Fecal-oral
Dirofilariosis	<i>Dirofilaria</i> spp.	Arthropod-borne
Diphyllobothriosis	<i>Diphyllobothrium latum</i>	Fish-borne
Foodborne trematodoses	<i>Fasciola</i> spp.; <i>Fasciolopsis buski</i>	Plant-borne
	<i>Opisthorchis</i> spp.; <i>Clonorchis sinensis</i>	Fish-borne
	<i>Paragonimus</i> spp.	Arthropod-borne
	Intestinal flukes	Various
Gnathostomosis	<i>Gnathostoma</i> spp.	Amphibian/reptile-borne
Sparganosis	<i>Spirometra</i> spp.	Amphibian/reptile-borne
Taeniosis	<i>Taenia</i> spp.	Meat-borne
Toxocarosis	<i>Toxocara</i> spp.	Fecal-oral (meat-borne)
Toxoplasmosis	<i>Toxoplasma gondii</i>	Fecal-oral, meat-borne
Trichinellosis	<i>Trichinella</i> spp.	Meat-borne
Zoonotic intestinal helminth infection	<i>Ascaris suum</i> ; <i>Trichuris</i> spp.	Fecal-oral
	<i>Ancylostoma</i> spp.; <i>Strongyloides stercoralis</i>	Fecal-oral, transcutaneous
Zoonotic intestinal protozoal infection	<i>Giardia duodenalis</i> ; <i>Cryptosporidium</i> spp.; <i>Blastocystis</i> spp.	Fecal-oral
	<i>Sarcocystis</i> spp.	Meat-borne
Zoonotic leishmaniosis	<i>Leishmania</i> spp. (excluding <i>L. donovani</i>)	Arthropod-borne
Zoonotic schistosomiasis	<i>Schistosoma japonicum</i>	Water-borne
Zoonotic trypanosomiasis	<i>Trypanosoma cruzi</i>	Arthropod-borne

*Less common transmission routes are shown in parentheses.

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information could be retrieved. Figure 2 presents a generic flow diagram of this applied search strategy.

Relevant data on study setting, diagnostic methods and study results were extracted from all eligible articles, and entered in spread sheet documents for further use.

Qualitative assessment

This initial assessment aimed at classifying the considered PZs according to their presumed endemicity status and data availability. To this end, we defined four categories:

- **Probably not endemic:** there is no direct or indirect local evidence and no direct evidence from neighboring countries;
- **Potentially endemic:** there is no direct or indirect local evidence, but there is direct evidence from neighboring countries; or, there is some direct local evidence, but of questionable nature, thus needing further confirmation;
- **Probably endemic & non-quantifiable:** there is direct or indirect local evidence; the burden cannot be quantified due to insufficient quantitative data or uncertainty in zoonotic potential or health effects;
- **Probably endemic & quantifiable:** there is direct or indirect local evidence; the burden can be quantified.

Additionally, information regarding the zoonotic nature of potentially zoonotic parasites was considered, with respect to alternative (dominant) anthroponotic transmission.

Quantitative assessment

Where possible, the prevalence of each PZ classified as “probably endemic & quantifiable” was modeled using a random effects meta-analysis in a Bayesian framework. In this model, it is assumed that the number of positive samples x_i in each study results from a binomial distribution with sample size n_i and a study-specific true prevalence θ_i , which is in its turn the result of an overall true prevalence π and a random study effect. The study effect is assumed to be normally distributed with mean zero and variance τ^2 . The prior distribution of τ^2 is Gamma with scale and shape parameter equal to 1, while a Normal distribution with mean 0 and precision 0.001 was used as prior for the logit-transformed true prevalence. Markov chain Monte Carlo methods are used to fit the model. More information on the meta-analysis model is provided in Supporting Information S2.

If data allowed, the health impact of the concerning PZs was also quantified as the number of incident cases, deaths and DALYs. The DALY metric is a summary measure of public health, widely used in disease burden assessments and cost-effectiveness analyses [6,7]. DALYs represent the overall number



Figure 1. Nepal, in red, bordered by India in the south, and China in the north.

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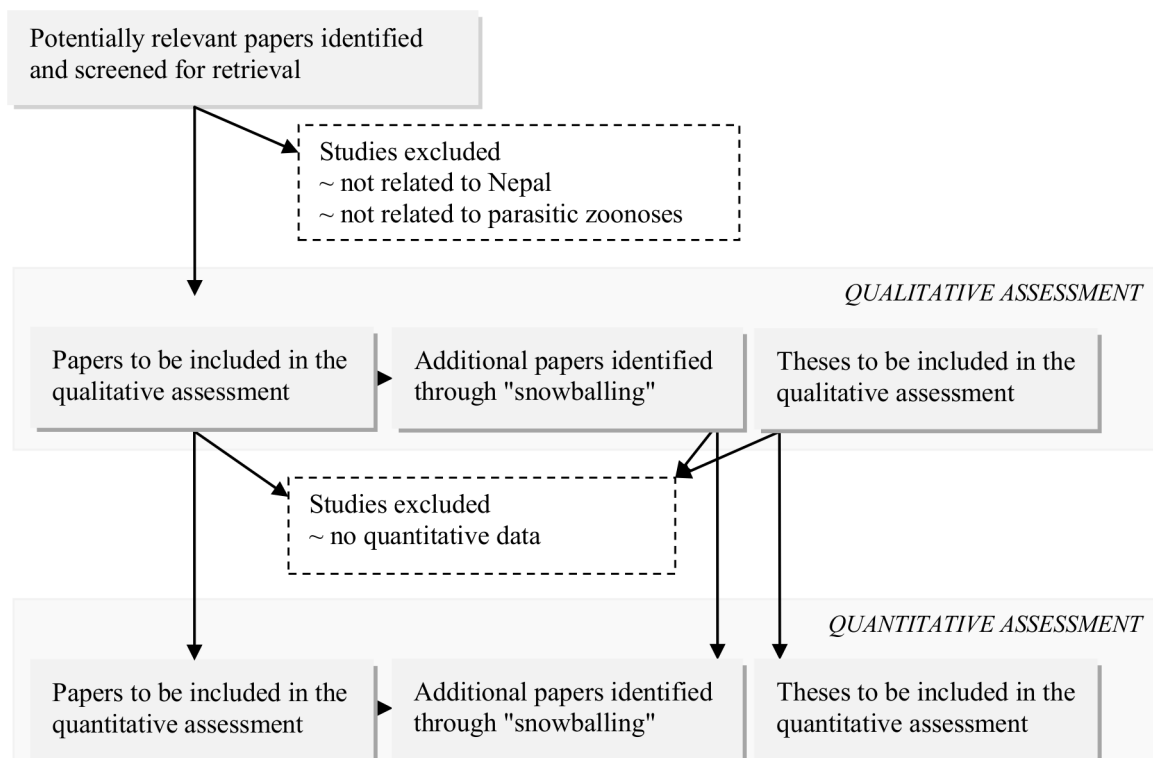


Figure 2. Generic flow diagram of applied search strategy.

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of healthy life years lost due to morbidity and mortality, hereby facilitating comparisons between diseases, and between countries and regions. The standard DALY formulas are:

$$\text{DALY} = \text{YLD} + \text{YLL}$$

$$\text{YLD} = \text{Number of cases} * \text{Duration} * \text{Disability Weight}$$

$$\text{YLL} = \text{Number of deaths} * \text{Life expectancy at age of death}$$

Calculation of DALYs was done using the standard formulas, and implemented in a fully stochastic framework using the DALY Calculator in R [15]. Supporting Information S3 presents the disease models and input distributions used for assessing the burden of the concerned PZs. We calculated undiscounted and unweighted DALYs, based on the Coale-Demeny model life table West, as our base case scenario. However, in order to enhance comparability of our estimates to estimates made by other authors, we performed scenario analyses by varying the time discount rate from 0% to 3%, by including age weighting, and by using the life expectancy table developed for the GBD 2010 study [7]. These different scenarios were denoted by $\text{DALY}_{\{K,r\}}$, with K equal to 0 for unweighted DALYs and equal to 1 for age-weighted DALYs, and with r the time discount rate. For all scenarios, results were calculated at the population level (i.e., absolute number of DALYs per year) and at the individual level (i.e., relative number of DALYs per symptomatic case). Incident cases, deaths and DALYs were calculated for reference year 2006, i.e., the midpoint of the eligible publication period, 2000–2012. The total population size for 2006 was calculated as the mean of the population sizes estimated in the 2001 and 2011 censuses. The age and sex distribution of the 2006 population was derived from the 2006 Nepal Demographic and Health Survey [16]. Table 2 presents the resulting population sizes used in the calculations.

Ethics statement

The data collection activities required for this study were approved by the ethical review board of the Nepal Health Research Council (Ramshahpath, Kathmandu, Nepal) and of the Ghent University Hospital (Ghent, Belgium; registration number B670201111932).

Results

Systematic review

For all twenty considered PZs, we identified 267 unique peer-reviewed documents and 50 unique dissertations. All identified documents were published in English. Table 3 summarizes the results of the systematic review for each considered PZ.

Table 2. 2006 age and sex specific population sizes used in the calculation of incident cases, deaths and DALYs.

	Male	Female	Total
0–4	1,766,025	1,673,583	3,439,608
5–14	3,655,548	3,556,364	7,211,913
15–44	4,668,234	6,331,723	10,999,957
45–59	1,259,682	1,464,385	2,724,068
60+	975,636	920,471	1,896,107
All ages	12,325,126	13,946,527	26,271,653

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Burden assessment

Table 4 presents the results of the qualitative classification of PZs. Out of the twenty considered PZs, only *Anisakidae* infection, zoonotic sleeping sickness (trypanosomosis) and zoonotic schistosomosis were classified as probably not endemic as no direct or indirect evidence was found. Seven PZs were classified as potentially endemic, i.e., alveolar echinococcosis, angiostrongylosis, capillariosis, dirofilariosis, gnathostomosis, sparganosis and cutaneous leishmaniosis. The ten remaining PZs were considered probably endemic, and the burden of three of these, neurocysticercosis, congenital (but not acquired) toxoplasmosis and cystic echinococcosis, could be fully quantified in terms of incident cases, deaths and DALYs.

Potentially endemic parasitic zoonoses. No local evidence could be found for alveolar echinococcosis, angiostrongylosis, capillariosis, dirofilariosis, gnathostomosis, sparganosis. However, recent case reports of these diseases in India indicate that these might be, or become, endemic in Nepal as well. Furthermore, some local evidence has been reported on zoonotic leishmaniosis, but this information remains unconfirmed. If any of these potentially endemic PZs are indeed endemic to Nepal, their burden is probably limited to a few sporadic cases.

So far, no cases of alveolar echinococcosis have been reported from Nepal, although a case of alveolar echinococcosis in a monk having traveled to Nepal, India, and Singapore has been reported [17]. However, given the considerable burden of alveolar echinococcosis in Tibetan communities [18], and the presence of putative cases from India [19,20,21], there are likely to be some cases in Nepal as well [22].

Human angiostrongylosis, capillariosis, dirofilariosis, gnathostomosis and sparganosis result from accidental infection with parasites that mainly have rodents, canines or felines as definitive hosts. The latter hosts are common in Nepal, and *Capillaria* eggs have already been identified in dog, cat and monkey stool samples and environmental samples [23,24,25,26,27,28], but it is unclear whether these were *C. aerophila*, or the clinically more important *C. hepatica* and *C. philippinensis*, which cause hepatic and intestinal capillariosis, respectively. Furthermore, *Spirometra* has been identified in stray dog stool samples from Kathmandu Valley [27], and Gewali [24] apparently found *Gnathostoma* eggs in water samples from Kathmandu. Human cases of these five PZs have not yet been reported from Nepal, but sporadic cases have been reported from India. Cases of eosinophilic meningitis due to *Angiostrongylus cantonensis* have been reported mainly from the southern Indian states [29,30]. Only few cases of human intestinal and hepatic capillariosis have been reported from India so far [31,32]. Ocular and subcutaneous manifestations of human dirofilariosis due to *Dirofilaria immitis* and *Dirofilaria repens* have been reported from southern states of India, but there have also been cases from the northern state of Punjab [33,34]. Barua et al. [35] reported a case of *Gnathostoma spinigerum* in a patient from the northeastern Indian state of Meghalaya, while Mukherjee et al. [36] present a case of cutaneous gnathostomosis in a female from the northeastern Indian state of Manipur. Some sparganosis case reports from India have been published, including cerebral [37], hepatic [38] and visceral manifestations, the latter in a patient from Uttar Pradesh [39].

It is widely recognized that Nepal is endemic for *Leishmania donovani*, the causative agent of anthroponotic visceral leishmaniosis (AVL), locally known as kala-azar [40,41,42]. Although some studies have hinted at a possible zoonotic transmission route of *L. donovani* [43,44,45], we considered kala-azar as a purely anthroponotic parasitic disease, and excluded it from the current study. In addition to AVL, however, several reports have presented cases

Table 3. Retrieved documents (total, retained).

Parasitic zoonosis	Total unique titles	Retained titles							
		Qualitative assessment				Quantitative assessment			
		Literature	Snowball	Thesis	Total	Literature	Snowball	Thesis	Total
Alveolar echinococcosis	3	1	0	0	1	0	0	0	0
Angiostrongylosis	3	0	0	0	0	0	0	0	0
<i>Anisakidae</i> infections	0	0	0	0	0	0	0	0	0
Capillariosis	7	2	0	4	6	0	0	0	0
Cystic echinococcosis	34	14	1	7	22	0	0	2	2
Cysticercosis	58	46	12	4	62	9	4	3	16
Diphyllobothriosis	1	0	0	3	3	0	0	0	0
Dirofilariosis	4	0	0	0	0	0	0	0	0
Foodborne trematodoses	22	2	4	5	11	0	0	0	0
Gnathostomosis	3	0	0	1	1	0	0	0	0
Sparganosis	3	1	0	0	1	0	0	0	0
Taeniosis	36	12	8	13	33	6	4	11	21
Toxocarosis	8	3	0	5	8	0	0	0	0
Toxoplasmosis	35	14	4	3	21	5	1	3	9
Trichinellosis	5	4	0	2	6	0	0	0	0
Zoonotic intestinal helminth infection	154	83	21	27	131	34	12	19	65
Zoonotic intestinal protozoal infection	114	62	24	23	109	36	12	16	64
Zoonotic leishmaniosis	242	17	1	1	19	0	0	0	0
Zoonotic schistosomosis	20	3	0	2	5	0	0	0	0
Zoonotic trypanosomosis	7	0	0	0	0	0	0	0	0

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of cutaneous leishmaniosis [46,47,48,49,50,51]. Although most of these cases have been imported, mostly from the Middle East, one report mentions a case of cutaneous leishmaniosis caused by *Leishmania major* in a woman not known to have lived outside Nepal [52,53,54]. The presence of *Phlebotomus papatasi*, a possible vector of *L. major* and *L. infantum* [43,55,56,57,58,59], further suggests that Nepal might be (or become) endemic for zoonotic leishmaniosis [60].

Probably endemic parasitic zoonoses. Trichinellosis has been confirmed in pigs, but never in humans in Nepal. Serological and/or coprological evidence of human infections with *Toxocara*, *Diphyllobothrium*, foodborne trematodes (FBT), and *Taenia* exists, but the population impact of these PZs is probably too low to quantify, although certain groups might be at high risk. Although

patent infections with intestinal helminths and protozoa are still very common, the health impact of zoonotic intestinal helminths and protozoa could not be assessed, due to uncertainty of zoonotic potential and health effects. On the other hand, the health impact of cysticercosis, toxoplasmosis and cystic echinococcosis was deemed quantifiable.

Trichinella infection has been serologically confirmed in pigs from Kathmandu [61,62], although Karn et al. [63] could not find seropositives in a sample of 344 pigs slaughtered in five districts of the Central Development Region of Nepal (including Kathmandu). Larvae have so far not yet been found on digestion. No human cases have been reported from Nepal, although Joshi et al. [61] mention the undocumented occurrence of sporadic cases of human trichinellosis reported from medical hospitals, and a

Table 4. Results of the qualitative assessment (in alphabetical order).

Probably endemic & quantifiable	Probably endemic & non-quantifiable	Potentially endemic	Probably not endemic
Cystic echinococcosis	Diphyllobothriosis	Alveolar echinococcosis	<i>Anisakidae</i> infections
Cysticercosis	Foodborne trematodoses	Angiostrongylosis	Zoonotic schistosomosis
Toxoplasmosis	Taeniosis*	Capillariosis	Zoonotic trypanosomosis
	Toxocarosis	Dirofilariosis	
	Trichinellosis	Gnathostomosis	
	Zoonotic intestinal helminth infections*	Sparganosis	
	Zoonotic intestinal protozoal infections*	Zoonotic leishmaniosis	

*For these parasitic zoonoses, prevalence estimates were available.

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trichinellosis outbreak has been documented from the north Indian state of Uttarakhand [64].

In a serological ELISA study, a high proportion of Nepalese people (~80%) appeared positive for *Toxocara* infection [65]. Recently, two children with eosinophilia were serodiagnosed with toxocarosis [66]. Furthermore, *Toxocara* spp. have been identified from dogs from Kathmandu [27,67,68], cats from Nawalparasi and Chitwan [26], and water samples from Kathmandu [24,25].

Diphylllobothrium has been found in dog stool samples from Kathmandu [67] and in the intestine of common carp fingerlings from a fish farm near Kathmandu [69]. Thapa [70] reports finding *Diphylllobothrium* eggs in the stools of 18/62 (29.0%) and 2/90 (2.2%) people of the Bote and Darai ethnic communities, respectively. Both are marginalized communities from Chitwan, and mainly depend on agriculture and fishing.

Some Nepali studies have reported trematode eggs in human and animal stools. Eggs of *Fasciola* spp. have been reported from buffaloes in a number of studies [71,72,73,74,75]. In community-based studies conducted in Kavre and Chitwan, *Fasciola* spp. eggs were reported in human stools [76,77]. In a study of diarrheal samples from Kathmandu, eggs resembling those of *Clonorchis sinensis* or *Opisthorchis* spp. were found [78,79]. However, as identification was based on visual identification only, confirmation is not certain. Three out of 84 children with eosinophilia presenting at a university hospital in Kavre were serologically positive for fasciolosis [66], while in another case series on eosinophilia in children, paragonimosis was suggested as a possible cause, given that a significant proportion of patients had the habit of eating undercooked fresh water crab meat [80]. In India, human cases of *Fasciolopsis buski* have been described from the Nepal bordering states of Bihar [81,82] and Uttar Pradesh [83].

Taeniosis, due to *Taenia solium*, *Taenia saginata* or *Taenia asiatica*, is commonly reported in Nepal. Different studies indicate low taeniosis prevalences in the general public and in clinical samples (<2%), although some papers hint at high prevalences in certain ethnic groups (10–50%) (Table S3-1 in Supporting Information S3). Higher taeniosis prevalence in certain groups is possible, as discussed by Prasad et al. [84] and Devleeschauwer et al. [85], although estimates of up to 50% are somewhat doubtful. Molecular studies have identified *T. asiatica* and *T. saginata* as causes of taeniosis [85,86], although it is to be expected that *T. solium* also causes taeniosis in Nepal, given its presence in animal intermediate hosts [87]. Apart from rare complications such as gastrointestinal obstruction or inflammation, the health impact of taeniosis is minimal. So far, there has only been one report describing such complications in a Nepalese patient [88]. As neither the national nor the international literature give a clear view of the probability of developing such complications, it was decided that the health impact could not be quantified.

A large number of studies have assessed the prevalence of intestinal helminths and protozoa in Nepal (Table S3-2 and S3-3 in Supporting Information S3). Community-based studies mainly targeted school children, while hospital-based studies were mostly set in large urban referral hospitals. Fewer studies looked at intestinal helminth and protozoal infestations in HIV-AIDS patients. However, a meaningful quantification of the public health impact of zoonotic intestinal helminths and protozoa was deemed impossible, due to the uncertainty regarding the extent to which these infections are truly zoonotic and the uncertainty regarding the health effects of zoonotic species [1]. Indeed, the limited available data suggest that intestinal helminth infections are mainly due to anthroponotic species. In the large study on genetic influences of helminth susceptibility in the Jirel population of Jiri, Dolakha, only *Ascaris lumbricoides* was reported [89,90]. Fecal

cultures to identify hookworm larvae so far only revealed the anthroponotic hookworm species *Ancylostoma duodenale* and *Necator americanus* [91,92]. The zoonotic relevance of intestinal protozoa remains less clear, even though genetic characterization of *Giardia* and *Cryptosporidium* from Nepal has been performed [93,94,95,96]. The zoonotic potential of *Blastocystis* appears to be best studied [97,98,99], yet there is large uncertainty about the prevalence of human infection given the limited number of studies, as well as substantial doubt regarding its pathogenic nature [100].

Human cysticercosis in Nepalese people has been described since the early 1990s, mainly through reports of patients with neurocysticercosis (NCC) [101,102,103,104,105,106,107,108,109,110,111], ocular cysticercosis [112,113,114,115,116] and muscular and soft tissue cysticercosis [117,118,119,120,121,122,123,124,125]. Its public health impact however did not receive full attention until the 2000s. Hospital-based studies indicate NCC prevalences in seizure patients ranging from 7% to 73% (Table S3-5 in Supporting Information S3). The majority of these studies applied neuroimaging. Two studies report the prevalence of NCC in hydrocephalus patients, indicating a prevalence of 1–2% [126,127], while a recent study indicates NCC prevalence of ~5% in patients with chronic headache [128]. A case series of three Nepalese intraventricular NCC patients molecularly identified the removed lesions as *T. solium* [129].

The majority of population-based studies on *Toxoplasma gondii* seroprevalence are from the 1990s [130,131,132,133,134], apart from two recent studies [135,136]. *T. gondii* seroprevalence has also been studied in women with bad obstetric history [137,138,139,140], patients with HIV/AIDS [139,141,142,143,144], ocular disorders [139] and hydrocephalus [126]. Apart from a recent case description [145], however, there appears to be no direct evidence on the impact of congenital toxoplasmosis, which is likely to represent the highest population burden [1]. As a result, it is only possible to obtain an indirect view of the impact of congenital toxoplasmosis in Nepal through population-based seroprevalence data.

Cystic echinococcosis has traditionally mostly been studied in livestock [27,146,147,148,149,150,151]. The few data in dogs indicate higher prevalence in areas where livestock has been slaughtered [149,152]. Since the 2000s, various case reports have been published on human hydatidosis [153,154,155,156,157,158,159,160,161]. Hospital register studies for CE cases have found low incidences [147,162,163]. So far, genotyping studies have revealed the presence of G1, the sheep strain in humans [164], dogs and livestock [149,165,166], G5 (cattle strain) in livestock [165] and G6 (camel strain) in humans [165].

Quantitative assessment. For intestinal infestations with *Taenia* spp., helminths and protozoa, we were able to estimate prevalence based on a random effects meta-analysis (Table 5). For neurocysticercosis, congenital toxoplasmosis and cystic echinococcosis we could estimate the number of incident cases, deaths and DALYs (Table 6; see Supporting Information S3 for more details on underlying data driving these estimates). Figure 3 visualizes the estimated burden at population and individual level, taking into account the uncertainty resulting from the parameter uncertainties, as suggested by Havelaar et al. [167]. Congenital toxoplasmosis has both a high population and patient burden, while neurocysticercosis is relatively less important at the patient level, but equally important at the population level. Cystic echinococcosis appears less important at both levels.

Discussion

As disease burden estimates are of increasing importance for policy making and evaluation, the need for such estimates becomes

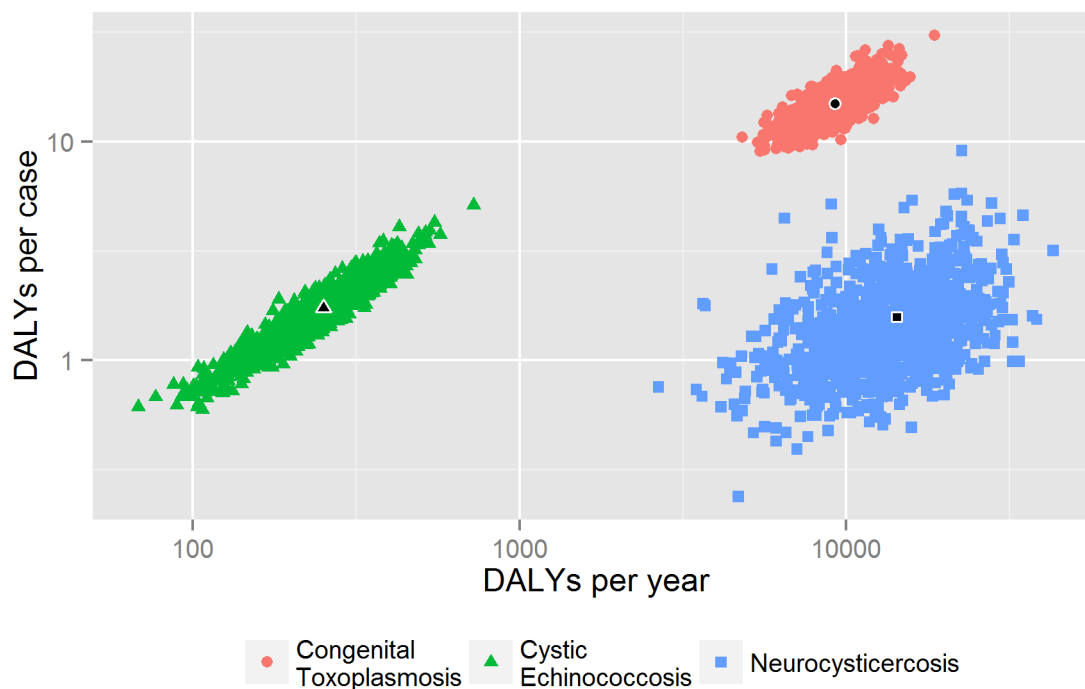


Figure 3. Population-level ($\text{DALYs}_{\{0,0\}}$ per year) versus individual-level burden ($\text{DALYs}_{\{0,0\}}$ per symptomatic case) in Nepal, 2006; the scatterplots represent 1000 random samples from each distribution, with the black symbol representing the centroid; both axes are on a log10 scale.

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eminent. In the late 1990s, the World Bank commissioned a comprehensive analysis of health care delivery in Nepal. Several recommendations were made for the further development of the Nepalese health sector, one of which was the establishment of priorities [168]. These recommendations were carried forward in the development of the *Nepal Health Sector Programmes* (NHSP), short-term strategic frameworks for the further development of the health sector. Since then, disease burden is recognized as one of the bases for setting program priorities [5]. However, when routine surveillance systems are performing poorly and baseline epidemiological studies are rare, these estimates are not readily available [169]. In this paper, we present the first comprehensive systematic review of the burden of PZs in Nepal. Information was sought from the international and national peer-reviewed scientific literature, and an important source of information was found in dissertations. The information found allowed qualitative assessment of the twenty PZs considered. However, quantitative estimates of prevalence or disease burden were possible for only a few.

Nepal is considered endemic for at least ten PZs, and might be endemic for seven others. Most of these diseases probably only have a small public health impact. However, neurocysticercosis and congenital toxoplasmosis are likely to impose an important burden to public health. Indeed, if we compare with the three “major” infectious diseases, we see that the estimated burden due to major clinical manifestations of three PZs, with in total 0.57 $\text{DALY}_{\{1,0.03\}}$ per 1000 people, is higher than that of the WHO 2004 GBD estimate for malaria (0.05 $\text{DALY}_{\{1,0.03\}}$ per 1000), comparable to that for HIV/AIDS (0.74 $\text{DALY}_{\{1,0.03\}}$ per 1000), but substantially lower than that for tuberculosis (5.45 $\text{DALY}_{\{1,0.03\}}$ per 1000) [6]. These comparisons suggest that greater attention for PZs in Nepal is warranted. Toxoplasmosis is for instance not reported in any official Nepalese data collection

system, and cysticercosis and toxoplasmosis were not considered in the WHO 2004 GBD update [6]. As a result, the incidence of congenital toxoplasmosis remains a critical data gap, and considerable uncertainties remain regarding the epilepsy prevalence and proportion of neurocysticercosis-associated epilepsy. Data on the zoonotic potential of intestinal helminths and protozoa and their health effects are lacking, although these infections may represent a considerable additional health burden.

In our study, certain methodological choices were made with as a consequence certain limitations. First, instead of applying strict inclusion/exclusion criteria, we aimed at collecting as much relevant information as possible. Inherently, this leads to large heterogeneity in the collected quantitative data. As a result, our burden estimates have large uncertainty intervals, making it for instance impossible to statistically distinguish the burden of neurocysticercosis and congenital toxoplasmosis. For congenital toxoplasmosis, as no direct evidence was available, we estimated the incidence based on a single age-specific seroprevalence study. Clearly, this puts an important constraint on the representativeness of our resulting burden estimate. Direct evidence on the incidence of congenital toxoplasmosis (e.g., through serological studies on newborns), preferably obtained through a multi-center study, is therefore needed to confirm our burden estimate.

Second, uncertainty was introduced by the selection and valuation of the clinical outcomes for the three diseases. We based our disease models on published studies [170–173], but note that other authors applied alternative ones. For instance, Bhattacharai et al. [174] also included severe headaches in their assessment of the burden of neurocysticercosis in Mexico, whereas this was deemed infeasible in our study. Likewise, the disability weights assigned to the different included clinical outcomes were derived from earlier studies [170–173], in order to enhance comparability with those studies. Nevertheless, other studies, including the GBD

Table 5. Quantitative assessment – occurrence of intestinal parasites.

Intestinal parasite	Number of datasets	Estimated prevalence (%)		
		Mean	95% Range*	Distribution
Community-based studies				
Taenia spp.	15	3.4	0.7–8.1	Beta(2.977, 84.058)
Ascaris spp.	37	15.6	10.6–21.4	Beta(26.936, 145.189)
Trichuris spp.	36	11.2	6.4–17.1	Beta(14.545, 115.807)
Hookworm	35	10.4	5.9–15.9	Beta(14.476, 125.337)
Giardia spp.	28	8.9	6.2–12.0	Beta(32.089, 330.444)
Cryptosporidium spp.	12	0.6	0.2–1.4	Beta(4.165, 641.569)
Blastocystis hominis	5	6.9	1.5–15.7	Beta(3.137, 42.457)
Hospital-based studies				
Taenia spp.	8	0.5	0.1–1.0	Beta(4.575, 977.996)
Ascaris spp.	25	3.4	1.8–5.5	Beta(12.621, 353.634)
Trichuris spp.	25	1.0	0.4–2.0	Beta(5.588, 550.789)
Hookworm	25	1.5	0.7–2.7	Beta(8.954, 577.751)
Giardia spp.	28	5.5	3.8–7.6	Beta(29.778, 507.152)
Cryptosporidium spp.	17	1.7	0.6–3.3	Beta(6.077, 352.688)
Blastocystis hominis	7	1.2	0.0–4.5	Beta(0.948, 77.444)
HIV-aids patients				
Ascaris spp.	4	2.1	0.0–9.2	Beta(0.671, 30.91)
Trichuris spp.	4	4.3	0.1–15.5	Beta(0.935, 21.065)
Hookworm	4	3.1	0.0–12.3	Beta(0.79, 24.688)
Giardia spp.	5	5.6	1.7–11.6	Beta(4.32, 73.437)
Cryptosporidium spp.	8	6.4	2.7–11.7	Beta(7.069, 102.905)
Blastocystis hominis	3	2.8	0.1–9.4	Beta(1.157, 40.646)

*Defined as the 2.5th and 97.5th percentile of the concerned distribution.
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Table 6. Quantitative assessment – disease impact*.

Parasitic zoonosis	Neurocysticercosis ^a	Congenital toxoplasmosis ^b	Cystic echinococcosis ^c	Total
Incident cases [95%CrI**]	—	1396 [1058–1780]	145 [114–179]	—
Incident symptomatic cases*** [95%CrI**]	10,618 [3304–22,296]	626 [473–813]	145 [114–179]	11,389 [4083–23,045]
Deaths [95%CrI**]	163 [39–378]	60 [27–105]	3 [0–7]	225 [93–442]
DALY_(0,0) [95%CrI**]	14,268 [5450–27,694]	9255 [6135–13,292]	251 [105–458]	23,773 [14,094–37,719]
DALY_{(0,0)/1000} [95%CrI**]	0.543 [0.207–1.054]	0.352 [0.234–0.506]	0.010 [0.004–0.017]	0.905 [0.536–1.436]
DALY_{(0,0)/symptomatic case} [95%CrI**]	1.581 [0.576–4.047]	14.934 [10.128–21.796]	1.741 [0.737–3.243]	—
DALY_(1,0.03) [95%CrI**]	10,924 [4270–21,301]	3964 [2648–5653]	204 [116–323]	15,092 [8215–25,546]
DALY_(0,0.03) [95%CrI**]	8916 [3569–17043]	3553 [2359–5098]	174 [96–277]	12,642 [7046–20,791]
DALY_{(0,0)–GBD2010 Life Expectancy} [95%CrI**]	14,994 [5668–29,273]	9673 [6347–14,017]	263 [106–486]	24,930 [14,706–39,702]

*Scenarios are denoted as DALY_(age weighting constant, discount rate).

**Credibility Interval.

***Incident symptomatic cases are the sum of all clinical manifestations across all incident cases.

^aThe clinical manifestations incorporated in the neurocysticercosis DALY estimates were epilepsy and death; note that the number of incident neurocysticercosis cases was not calculated, as the estimation started from the incidence of epilepsy (see Supporting Information S3).

^bThe clinical manifestations incorporated in the congenital toxoplasmosis DALY estimates were chorioretinitis at birth, chorioretinitis later in life, hydrocephalus, intracranial calcifications, central nervous system abnormalities, fetal death and neonatal death.

^cThe clinical manifestations incorporated in the cystic echinococcosis DALY estimates were post-surgical recovery (with rehabilitation and possible worrying), substantial post-surgical conditions, post-surgical recurrent disease, post-surgical death, and an average health state for non-reported cases; no burden was attributed to healthcare seeking cases that were not treated surgically.

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studies, are less transparent about their applied disease models and disability weights, impeding unambiguous comparisons. For instance, the GBD 2010 study estimated the number of DALY_{0,0} in Nepal to be 667 [141–2073] for “echinococcosis” and 4220 [2786–6022] for cysticercosis [175]. Given a lack of knowledge on the disease models, disability weights and data behind these estimates, it is difficult to assess the reason for any differences or similarities with our estimates. Toxoplasmosis and other PZs appear to be absent from the GBD 2010 study.

Third, subjective methodological choices regarding the calculation of DALYs may lead to further uncertainty. We tried to deal with this source of uncertainty by calculating DALYs under different common sets of normative assumptions, i.e., no discounting and age weighting, 3% time discounting and no age weighting, 3% time discounting and age weighting; and by calculating DALYs based on both the Coale-Demeny model life table West and the new GBD 2010 life expectancy table. As expected, time discounting led to smaller burden estimates. The difference between both life tables was minimal.

In addition, this study focused on the population burden of PZs. Some PZs, however, might have an important individual burden, even though their population burden is negligible or small. Likewise, the burden suffered by specific sub-populations (e.g., caste or ethnic groups), might be much higher than average population burden [85].

Finally, due to a lack of time and resources, we had to place restrictions on the nature of the diseases to be studied, and on the nature of the burden estimates to be generated. Indeed, this study only focuses on the burden of *parasitic* zoonoses. However, as means for interventions are poor, future integrated control should be packaged by, for instance, simultaneously controlling cystic echinococcosis, brucellosis and rabies. This analysis should therefore be extended to the burden of bacterial and viral zoonoses in Nepal. By quantifying the burden in terms of incidence, mortality and DALYs, we also focused on the *health* impact of the concerned diseases. Some PZs might have an important economic impact, for example in terms of livestock health, or might reduce psycho-social wellbeing in a way not captured by the applied metrics. Truly evidence-informed priority setting and decision making should take in account all these aspects of disease burden, implying that our estimates should be complemented by others.

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Despite these limitations, this study has identified the most important PZs for Nepal, as far as existing data allows. The quantitative estimates of disease burden for three of these diseases suggest that PZs deserve greater attention and more intensive surveillance. As population and disease transmission dynamics change over time, disease burden changes dynamically as well. Therefore, the presented results should be updated regularly, and this exercise should be extended to other groups of neglected diseases or even to a full national burden of disease study. We therefore hope that this study will stimulate further research, so that the overall human health burden in Nepal can be better characterized. In the long term, however, continued efforts to improve surveillance and database system at the local level should enable truly monitoring of disease burden over time.

Supporting Information

Checklist S1 PRISMA checklist. (DOC)

Supporting Information S1 Search strategy. (DOC)

Supporting Information S2 Bayesian random-effects meta-analysis. (DOC)

Supporting Information S3 Quantitative burden assessment. (DOCX)

Acknowledgments

We would like to dedicate this manuscript to the memory of Dr Durga Datt Joshi, who passed away on 25 November 2013. Dr Joshi was the pioneer researcher in the field of veterinary public health in Nepal. Long before the advent of DALYs, Dr Joshi realized the importance of zoonotic diseases, and significantly contributed to our current understanding of their epidemiology and impact.

Author Contributions

Conceived and designed the experiments: BD LD PD NS. Performed the experiments: BD AA BDP SBP DDJ. Analyzed the data: BD PT NP CMdN RLJV AHH LD PD NS. Contributed reagents/materials/analysis tools: BD AA PT NP CMdN BDP SBP RL JV DDJ AHH LD PD NS. Wrote the paper: BD AA PT NP CMdN BDP SBP RL JV DDJ AHH LD PD NS.

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